```
Logging in to Dialog

Trying 9158046...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ********
ENTER PASSWORD:
 bwt0kvzc
 ********
Welcome to DIALOG

Dialog level 99.02.26D

Last logoff:  15mar99 19:26:50
Logon file405 18mar99 14:31:55
ANNOUNCEMENT    ****    ANNOUNCEMENT    ****    ANNOUNCEMENT
NEW
***Miller Freeman Industry and Product News (File 112)
***Irish Times (File 477)
***Business Wire (Files 610 for current news & 810 for archive news)
***Financial Times Abstracts (File 473)
                          ***
RELOADED
***HealthSTAR (File 151)
***Aidsline (File 157)
***Medline (Files 154,155)
***EMBASE (Files 72,73)
***CLAIMS/U.S. Patents (Files 340, 341, 942) dialog

***BIOSIS Previews (File 5,55)- enhanced 11/16/98, see HELP NEWS5
***Claims Reassignment/Reexamination (File 123)
                          ***
REMOVED
***Disclosure Database, File 100, removed 1/31/99
***Technimetrics Executive Directory, File 552,
   removed effective 1/31/99
                          ***
DIALINDEX
***DIALINDEX categories have been revised. For listing of new/revised
   categories see http://library.dialog.com/bluesheets/html/blo.html.
   For more details, see HELP NEWS411.

     >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
     >>>    of new databases, price changes, etc.      <<<
***** The DIALORDER suppliers DYNAMIC and FILEDOC are no longer  *****
***** in business. Please do not use them.                       *****
*****                                                           *****
*****File 265:  Please use file 266 as file 265 is no longer     *****
*****  available.                                               *****
***** The MASIS DIALORDER service has been discontinued. For     *****
*****
***** details, please contact MARUZEN CO. LTD, at 3-3272-3496.   *****

***** Files 100 and 552 have been removed from DIALOG.           *****
***** NEW CURRENT year ranges installed.                         *****
*****                                                           *****
SYSTEM:HOME
Menu System II: D2 version 1.7.8 term=ASCII
```

*** DIALOG HOMEBASE(SM) Main Menu ***

Information:
 1. Announcements (new files, reloads, etc.)
 2. Database, Rates, & Command Descriptions
 3. Help in Choosing Databases for Your Topic
 4. Customer Services (telephone assistance, training, seminars, etc.)
 5. Product Descriptions

Connections:
 6. DIALOG(R) Document Delivery
 7. Data Star(R)

/H = Help /L = Logoff /NOMENU = Command Mode

Enter an option number to view information or to connect to an online service. Enter a BEGIN command plus a file number to search a database (e.g., B1 for ERIC).
? b 410

>>Invalid Option Number

*** DIALOG HOMEBASE(SM) Main Menu ***

Information:
 1. Announcements (new files, reloads, etc.)
 2. Database, Rates, & Command Descriptions
 3. Help in Choosing Databases for Your Topic
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Connections:
 6. DIALOG(R) Document Delivery
 7. Data Star(R)

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/H = Help /L = Logoff /NOMENU = Command Mode

Enter an option number to view information or to connect to an online service. Enter a BEGIN command plus a file number to search a database (e.g., B1 for ERIC).
? set hi **;set hi**

18mar99 14:32:09 User242957 Session D22.1
$0.00 0.160 DialUnits FileHomeBase
$0.00 Estimated cost FileHomeBase
FTSNET 0.004 Hrs.
$0.00 Estimated cost this search
$0.00 Estimated total session cost 0.160 DialUnits

File 410:Chronolog(R) 1981-1999 Mar/Apr
(c) 1999 The Dialog Corporation plc

Set	Items	Description

```
?
HILIGHT set on as ''
HILIGHT set on as ''
? b 155, 5

       18mar99 14:32:19 User242957 Session D22.2
            $0.00    0.058 DialUnits File410
     $0.00  Estimated cost File410
            FTSNET   0.002 Hrs.
     $0.00  Estimated cost this search
     $0.00  Estimated total session cost   0.218 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-1999/May W1
         (c) format only 1999 Dialog Corporation
*File 155: reloaded, note accession numbers changed.
  File   5:BIOSIS PREVIEWS(R)  1969-1999/Mar W3
         (c) 1999 BIOSIS

      Set  Items  Description
      ---  -----  -----------
? e au=young, judy carol


Ref   Items  Index-term
E1        2  AU=YOUNG-YANG S
E2        1  AU=YOUNG-ZINECKER E
E3        0 *AU=YOUNG, JUDY CAROL
E4        1  AU=YOUNG, SN
E5        1  AU=YOUNGA A
E6        1  AU=YOUNGA G
E7        2  AU=YOUNGASH RN
E8        6  AU=YOUNGBAR P
E9        3  AU=YOUNGBAR P R
E10       1  AU=YOUNGBAR PR
E11       3  AU=YOUNGBERG A
E12       4  AU=YOUNGBERG A D

          Enter P or PAGE for more
? e au=young, jc


Ref   Items  Index-term
E1        2  AU=YOUNG-YANG S
E2        1  AU=YOUNG-ZINECKER E
E3        0 *AU=YOUNG, JC
E4        1  AU=YOUNG, SN
E5        1  AU=YOUNGA A
E6        1  AU=YOUNGA G
E7        2  AU=YOUNGASH RN
E8        6  AU=YOUNGBAR P
E9        3  AU=YOUNGBAR P R
E10       1  AU=YOUNGBAR PR
E11       3  AU=YOUNGBERG A
E12       4  AU=YOUNGBERG A D

          Enter P or PAGE for more
? e au= young judy
```

```
Ref    Items  Index-term
E1         4 *AU=YOUNG JUDY
E2         3  AU=YOUNG JUDY C
E3         2  AU=YOUNG JUDY T
E4         2  AU=YOUNG JULIA
E5         3  AU=YOUNG JULIA C
E6         2  AU=YOUNG JULIANA
E7         1  AU=YOUNG JULIE
E8         8  AU=YOUNG JV
E9       157  AU=YOUNG JW
E10        1  AU=YOUNG JW 3D
E11       47  AU=YOUNG JZ
E12      247  AU=YOUNG K

          Enter P or PAGE for more
? s e1 or e2

               4  AU=YOUNG JUDY
               3  AU=YOUNG JUDY C
      S1       7  AU="YOUNG JUDY" OR AU="YOUNG JUDY C"
? e au=young jc


Ref    Items  Index-term
E1         7  AU=YOUNG JAY A
E2       307  AU=YOUNG JB
E3       118 *AU=YOUNG JC
E4       456  AU=YOUNG JD
E5        48  AU=YOUNG JD JR
E6        57  AU=YOUNG JE
E7         1  AU=YOUNG JEAN W
E8         2  AU=YOUNG JEANNE E
E9         6  AU=YOUNG JEFF C
E10        2  AU=YOUNG JEFF L
E11        1  AU=YOUNG JEFFERY E
E12        4  AU=YOUNG JEFFREY

          Enter P or PAGE for more
? s e3

      S2     118  AU="YOUNG JC"
? e au=murray, lesley jean


Ref    Items  Index-term
E1         2  AU=MURRAY-WHELAN ROSEMARY
E2         4  AU=MURRAY-WILSON A
E3         0 *AU=MURRAY, LESLEY JEAN
E4         1  AU=MURRAYAMA J-I
E5         1  AU=MURRAYD D R
E6         1  AU=MURRAYI J L II
E7         1  AU=MURRAYS FE
E8        82  AU=MURRE C
E9         1  AU=MURRE COMELIS
E10       29  AU=MURRE CORNELIS
E11        2  AU=MURRE J M J
E12        1  AU=MURRE JAAP M J

          Enter P or PAGE for more
? e au=murray, l j
```

```
Ref   Items  Index-term
E1        2  AU=MURRAY-WHELAN ROSEMARY
E2        4  AU=MURRAY-WILSON A
E3        0 *AU=MURRAY, L J
E4        1  AU=MURRAYAMA J-I
E5        1  AU=MURRAYD D R
E6        1  AU=MURRAYI J L II
E7        1  AU=MURRAYS FE
E8       82  AU=MURRE C
E9        1  AU=MURRE COMELIS
E10      29  AU=MURRE CORNELIS
E11       2  AU=MURRE J M J
E12       1  AU=MURRE JAAP M J

          Enter P or PAGE for more
? s au=murray leslie jean

      S3       0  AU=MURRAY LESLIE JEAN
? e au=murray leslie jean


Ref   Items  Index-term
E1        5  AU=MURRAY LESLEY
E2        9  AU=MURRAY LESLEY J
E3        0 *AU=MURRAY LESLIE JEAN
E4        2  AU=MURRAY LEYTON
E5        2  AU=MURRAY LF
E6        8  AU=MURRAY LG
E7        2  AU=MURRAY LIAM J
E8        1  AU=MURRAY LILIAN
E9        5  AU=MURRAY LILIAN S
E10       1  AU=MURRAY LILLIAN
E11       4  AU=MURRAY LINDA
E12       2  AU=MURRAY LINDSAY

          Enter P or PAGE for more
? s e1 and e2

               5  AU=MURRAY LESLEY
               9  AU=MURRAY LESLEY J
      S4       0  AU="MURRAY LESLEY" AND AU="MURRAY LESLEY J"
? e au=murray lj


Ref   Items  Index-term
E1        1  AU=MURRAY LINDSEY
E2        1  AU=MURRAY LISA J
E3       32 *AU=MURRAY LJ
E4        4  AU=MURRAY LL
E5       17  AU=MURRAY LM
E6        4  AU=MURRAY LN
E7        1  AU=MURRAY LOIS E
E8        1  AU=MURRAY LORNA A
E9        1  AU=MURRAY LOUISE A S
E10      29  AU=MURRAY LP
E11       2  AU=MURRAY LR
E12      16  AU=MURRAY LS
```

```
          Enter P or PAGE for more
? s e3

      S5      32  AU="MURRAY LJ"
? ds


Set     Items   Description
S1          7   AU="YOUNG JUDY" OR AU="YOUNG JUDY C"
S2        118   AU="YOUNG JC"
S3          0   AU=MURRAY LESLIE JEAN
S4          0   AU="MURRAY LESLEY" AND AU="MURRAY LESLEY J"
S5         32   AU="MURRAY LJ"
? e au=tushinski, robert j


Ref   Items  Index-term
E1       20  AU=TUSHINSKI RJ
E2        4  AU=TUSHINSKI ROBERT
E3        0 *AU=TUSHINSKI, ROBERT J
E4        7  AU=TUSHISHVILI D G
E5        5  AU=TUSHISHVILI D I
E6        3  AU=TUSHISHVILI DG
E7        2  AU=TUSHISHVILI DI
E8        9  AU=TUSHISHVILI L SH
E9        2  AU=TUSHKANOVÀ M V
E10       2  AU=TUSHKANOVA MV
E11       1  AU=TUSHKIN V V
E12       1  AU=TUSHKIN VV

          Enter P or PAGE for more
? s e1 and e2

             20  AU=TUSHINSKI RJ
              4  AU=TUSHINSKI ROBERT
      S6      0  AU="TUSHINSKI RJ" AND AU="TUSHINSKI ROBERT"
? s e1 or e2

             20  AU=TUSHINSKI RJ
              4  AU=TUSHINSKI ROBERT
      S7     24  AU="TUSHINSKI RJ" OR AU="TUSHINSKI ROBERT"
? e au=tushinski robert j


Ref   Items  Index-term
E1       20  AU=TUSHINSKI RJ
E2        4  AU=TUSHINSKI ROBERT
E3        0 *AU=TUSHINSKI ROBERT J
E4        7  AU=TUSHISHVILI D G
E5        5  AU=TUSHISHVILI D I
E6        3  AU=TUSHISHVILI DG
E7        2  AU=TUSHISHVILI DI
E8        9  AU=TUSHISHVILI L SH
E9        2  AU=TUSHKANOVA M V
E10       2  AU=TUSHKANOVA MV
E11       1  AU=TUSHKIN V V
E12       1  AU=TUSHKIN VV

          Enter P or PAGE for more
? e au=murray leslie jean
```

```
Ref    Items  Index-term
E1         5  AU=MURRAY LESLEY
E2         9  AU=MURRAY LESLEY J
E3         0 *AU=MURRAY LESLIE JEAN
E4         2  AU=MURRAY LEYTON
E5         2  AU=MURRAY LF
E6         8  AU=MURRAY LG
E7         2  AU=MURRAY LIAM J
E8         1  AU=MURRAY LILIAN
E9         5  AU=MURRAY LILIAN S
E10        1  AU=MURRAY LILLIAN
E11        4  AU=MURRAY LINDA
E12        2  AU=MURRAY LINDSAY

          Enter P or PAGE for more
? s e1 or e2

                5  AU=MURRAY LESLEY
                9  AU=MURRAY LESLEY J
      S8       14  AU="MURRAY LESLEY" OR AU="MURRAY LESLEY J"
? ds


Set     Items   Description
S1          7   AU="YOUNG JUDY" OR AU="YOUNG JUDY C"
S2        118   AU="YOUNG JC"
S3          0   AU=MURRAY LESLIE JEAN
S4          0   AU="MURRAY LESLEY" AND AU="MURRAY LESLEY J"
S5         32   AU="MURRAY LJ"
S6          0   AU="TUSHINSKI RJ" AND AU="TUSHINSKI ROBERT"
S7         24   AU="TUSHINSKI RJ" OR AU="TUSHINSKI ROBERT"
S8         14   AU="MURRAY LESLEY" OR AU="MURRAY LESLEY J"
? s s1 or s2 or s5 or s7 or s8

                7  S1
              118  S2
               32  S5
               24  S7
               14  S8
      S9      190  S1 OR S2 OR S5 OR S7 OR S8
? s l9 and expan? and hematopoietic and stem and cell

              344  L9
           114350  EXPAN?
            57698  HEMATOPOIETIC
           162121  STEM
          2980518  CELL
     S10        0  L9 AND EXPAN? AND HEMATOPOIETIC AND STEM AND CELL
? s l9 and hematopoietic and stem and cell

              344  L9
            57698  HEMATOPOIETIC
           162121  STEM
          2980518  CELL
     S11        0  L9 AND HEMATOPOIETIC AND STEM AND CELL
? s l9 and stem and cell

              344  L9
```

```
          162121  STEM
         2980518  CELL
     S12       1  L9 AND STEM AND CELL
? d ti,ab

>>>',' not a valid keyword
? t s12/3,ab/1


 12/3,AB/1     (Item 1 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
(c) 1999 BIOSIS. All rts. reserv.

09163763   BIOSIS NO.: 199497172133
Visualization of protein-nucleic acid interactions involved in the in vitro
  assembly of the Escherichia coli 50 S ribosomal subunit.

AUTHOR: Tumminia Santa J(a); Hellmann Wilhelmine; Wall Joseph S; Boublik
  Miloslav
AUTHOR ADDRESS: (a)Roche Inst. Mol. Biol., Roche Res. Cent., Nutley, NJ
  07110, USA

JOURNAL: Journal of Molecular Biology  235 (4):p1239-1250 1994
ISSN: 0022-2836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein-nucleic acid interactions which occur during Escherichia
  coli 50 S ribosomal subunit assembly between 23 S rRNA, 5 S rRNA and a
  complete set of 34 L-proteins were monitored by high resolution scanning
  transmission electron microscopy (STEM). This approach made it
  possible to visualize and quantitatively analyze conformational changes
  induced in the rRNAs during E. coli 50 S ribosomal subunit assembly. The
  reconstituted RNA-protein complexes, the control 23 S rRNA and native 50
  S subunits were characterized by their mass and morphology. Association
  of 23 8 rRNA with the first assembly protein, L24, led to the formation
  of a distinct nucleus of mass ("cluster") on the filamentous and loosely
  coiled molecule of the 23 S rRNA. This structural feature was preserved
  and enhanced in 23 S rRNA after its association with the rest of the
  early assembly proteins, namely L3, L20, L13, L4 and L22. Since the above
  proteins, with the exception of L3, bind to the 5' end of the 23 S rRNA,
  the cluster seems to be formed predominantly by interactions of L24, L13,
  L20, L22 and L4 with this segment of the 23 S rRNA molecule. Association
  with the rest of the primary binding proteins (L2, L23, L9, L1),
  which interact with the 3' end of the 23 S rRNA, appears to result in the
  formation of a second mass center. Binding of additional proteins led to
  the formation of compact particles with an apparent similarity to the 50
  S subunit. However, particles with defined structural features
  characteristic of the native 50 S subunit requires the interactions of
  both 23 S rRNA and 5 S rRNA with all of the L-proteins. STEM image
  analysis demonstrated that 50 S subunit reconstitution proceeds by the
  immediate folding of the 23 S rRNA into a single mass center followed by
  the formation of a second mass center. These mass centers merge into one
  central body, which is gradually enhanced and decorated with structural
  elements characteristic of the 50 S subunit in the latter stages of
  assembly.
? log y

    18mar99 14:42:59 User242957 Session D22.3
```

```
        $1.38    0.461 DialUnits File155
    $1.38  Estimated cost File155
        $3.66    0.696 DialUnits File5
           $1.55  1 Type(s) in Format  4 (UDF)
        $1.55  1 Types
    $5.21  Estimated cost File5
        OneSearch, 2 files,  1.157 DialUnits FileOS
        FTSNET   0.183 Hrs.
    $6.59  Estimated cost this search
    $6.59  Estimated total session cost   1.375 DialUnits
Logoff: level 99.02.26 D  14:42:59


Trying 01082...Open

PLEASE ENTER HOST PORT ID:
PLEASE ENTER HOST PORT ID:x
LOGINID:d160mms
PASSWORD:
TERMINAL (ENTER 1, 2, 3, 4, OR ?): 3


  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
  *                                                               *
  *           Welcome to MESSENGER (APS Text) at USPTO            *
  *                                                               *
  *                                                               *
  *    The USPTO production files are current through:            *
  *    MARCH 16,1999  for U.S. Patent Text Data.             *
  *    MARCH 16,1999  for U.S. Current Classification Data.  *
  *    MARCH 16,1999  for U.S. Patent Image Data.            *
  *                                                               *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
     AFTER PRODUCTION HOURS (AT 10:00 P.M.) ON WEDNESDAY, 01/27/99,
     SEVERAL PTONET DEVICES WILL BE RECONFIGURED TO ENHANCE
     NETWORK OPERATIONS.  USERS OF PATENT EXAMINER SEARCH TOOLS
     MUST RE-BOOT THEIR INDIVIDUAL DESKTOP WORKSTATIONS AT THE
     START OF THE BUSINESS DAY ON THURSDAY, 01/28/99 TO INSURE
     THAT NECESSARY FILES ON THEIR WORKSTATION GET UPDATED.  THIS
     WILL ENSURE IMMEDIATE AND ACCURATE ACCESS TO ALL OF THE
     PATENT EXAMINER SEARCH TOOLS.  THANK YOU FOR YOUR COOPERATION
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
  *       * PLEASE USE 305-9000 FOR NEW TELEPHONE NUMBER *       *
  *                                                               *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
  * More U.S. patent data is now available on APS.  The new      *
  * USOCR file contains patents issued in 1970, plus some        *
  * patents that were missing from the USPAT file.  See the      *
  * Patents News Folder under the Public Folders in e-mail for   *
  * more information on using the new file.  Thank you.          *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
  *  DISCLAIMER:                                                  *
  *  Neither the United States Government, nor any agency         *
  *  thereof, nor any of their contractors, subcontractors or     *
  *  employees make any warranty, expressed or implied,           *
  *  including any warranty of marketability of fitness for a     *
  *  particular purpose; nor assumes any legal liability or       *
  *  responsibility for any party's use, or the results of        *
  *  such, of the data.                                           *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
```

```
  *                Help Desk --> 703-305-9000                      *
  *                                                                *
  *    The Help Desk is staffed for APS support 7 days/week.       *
  *      Monday through Friday:      6:30am - 9:00pm               *
  *      Saturday, Sunday, Holidays: 8:30am - 5:00 pm              *
  *                                                                *
  *    The Help Desk staff at this number will handle all APS      *
  *    related questions.                                          *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
  *    >>>>>>>>>>>>> NEW SUNDAY HOURS !!! <<<<<<<<<<<<<            *
  *                                                                *
  *    The APS is available:                                       *
  *            6:30am - 9:00pm Monday through Friday               *
  *            7:30am - 5:00pm Saturday, Sunday, Holidays          *
  *                                                                *
  *      APS is unavailable Thanksgiving Day, Christmas Day,       *
  *      and New Year's Day.                                       *
  *                                                                *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
FILE 'USPAT' ENTERED AT 14:40:27 ON 18 MAR 1999

  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
  *              W E L C O M E   T O   T H E                       *
  *         U. S.   P A T E N T   T E X T   F I L E                *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

=> s hematopoietic and stem and cell and culture

          2401 HEMATOPOIETIC
             9 HEMATOPOIETICS
          2402 HEMATOPOIETIC
                 (HEMATOPOIETIC OR HEMATOPOIETICS)
         90032 STEM
         27615 STEMS
        103541 STEM
                 (STEM OR STEMS)
        226133 CELL
        183427 CELLS
        269705 CELL
                 (CELL OR CELLS)
         51427 CULTURE
         28066 CULTURES
         56220 CULTURE
                 (CULTURE OR CULTURES)
L1        1164 HEMATOPOIETIC AND STEM AND CELL AND CULTURE

=> s l1 and method and (increase or expand or enlarge or grow?) (2a) cell (w)
(volume or amount or number)

       1210282 METHOD
        663773 METHODS
       1302241 METHOD
                 (METHOD OR METHODS)
        810546 INCREASE
        542687 INCREASES
       1010747 INCREASE
                 (INCREASE OR INCREASES)
         99998 EXPAND
         59785 EXPANDS
        135630 EXPAND
```

```
                (EXPAND OR EXPANDS)
          21862 ENLARGE
           7073 ENLARGES
          27545 ENLARGE
                (ENLARGE OR ENLARGES)
         221307 GROW?
         226133 CELL
         183427 CELLS
         269705 CELL
                (CELL OR CELLS)
         506547 VOLUME
          89173 VOLUMES
         524130 VOLUME
                (VOLUME OR VOLUMES)
        1112383 AMOUNT
         432297 AMOUNTS
        1176748 AMOUNT
                (AMOUNT OR AMOUNTS)
        1245502 NUMBER
         264137 NUMBERS
        1290408 NUMBER
                (NUMBER OR NUMBERS)
            515 (INCREASE OR EXPAND OR ENLARGE OR GROW?) (2A) CELL (W) (VOL
UME
                 OR AMOUNT OR NUMBER)
L2           66 L1 AND METHOD AND (INCREASE OR EXPAND OR ENLARGE OR GROW?)
(2A
                ) CELL (W) (VOLUME OR AMOUNT OR NUMBER)

=> s l2 and ((thrombopoietin or TPO) or flt3 or (interleukin (w) 6 or IL6))

             123 THROMBOPOIETIN
               1 THROMBOPOIETINS
             123 THROMBOPOIETIN
                 (THROMBOPOIETIN OR THROMBOPOIETINS)
             695 TPO
              93 TPOS
             758 TPO
                 (TPO OR TPOS)
              26 FLT3
            5449 INTERLEUKIN
            1679 INTERLEUKINS
            6289 INTERLEUKIN
                 (INTERLEUKIN OR INTERLEUKINS)
         2195085 6
             688 INTERLEUKIN (W) 6
             166 IL6
L3           20 L2 AND ((THROMBOPOIETIN OR TPO) OR FLT3 OR (INTERLEUKIN (W)
 6
                OR IL6))

=> s l3 and ((interleukin 3 or il3) or (leukemia inhibitory factor or lif) or
c-kit

UNMATCHED LEFT PARENTHESIS 'AND ((INTERLEUK'

=> s l3 and ((interleukin 3 or il3) or (leukemia inhibitory factor or lif) or
c-kit)

            5449 INTERLEUKIN
```

```
          1679 INTERLEUKINS
          6289 INTERLEUKIN
                 (INTERLEUKIN OR INTERLEUKINS)
       2405822 3
           585 INTERLEUKIN 3
                 (INTERLEUKIN(W)3)
           215 IL3
          9247 LEUKEMIA
          2021 LEUKEMIAS
          9888 LEUKEMIA
                 (LEUKEMIA OR LEUKEMIAS)
         25550 INHIBITORY
        265364 FACTOR
        238734 FACTORS
        416419 FACTOR
                 (FACTOR OR FACTORS)
           231 LEUKEMIA INHIBITORY FACTOR
                 (LEUKEMIA(W)INHIBITORY(W)FACTOR)
          2258 LIF
            19 LIFS
          2269 LIF
                 (LIF OR LIFS)
       1325462 C
         30347 KIT
         10040 KITS
         33140 KIT
                 (KIT OR KITS)
           219 C-KIT
                 (C(W)KIT)
L4          16 L3 AND ((INTERLEUKIN 3 OR IL3) OR (LEUKEMIA INHIBITORY FACT
OR
                 OR LIF) OR C-KIT)

=> d 14 ti,ab 1-16


US PAT NO:      5,861,315 [IMAGE AVAILABLE]             L4: 1 of 16
TITLE:          Use of **stem** **cell** factor and soluble
                  **interleukin**-**6** receptor for the ex vivo expansion
                  of **hematopoietic** multipotential **cells**

ABSTRACT:
**Stem** **cell** factor in combination with soluble **interleukin**-
**6** receptor, **interleukin**-**6**, for gp130 signaling, supports the
proliferation, differentiation and terminal maturation of blood **cells**
from normal human **hematopoietic** multipotential **cells**.

US PAT NO:      5,851,984 [IMAGE AVAILABLE]             L4: 2 of 16
TITLE:          **Method** of enhancing proliferation or differentiation
                  of **hematopoietic** **stem** **cells** using Wnt
                  polypeptides

ABSTRACT:
Uses for Wnt polypeptides in hematopoiesis are disclosed. In particular,
in vitro and in vivo **methods** for enhancing proliferation or
differentiation of a **hematopoietic** **stem**/progenitor **cell** using
a Wnt polypeptide, and optionally another cytokine, are described.

US PAT NO:      5,846,529 [IMAGE AVAILABLE]             L4: 3 of 16
TITLE:          Infusion of neutrophil precursors for treatment of
```

neutropenia

ABSTRACT:
The invention provides a **method** of treating a patient having a reduced population of neutrophils following a myeloablative cancer treatment such as high dose chemotherapy. Following myeloablative therapy, a **cell** composition of at least 25% neutrophil precursors, i.e. promyelocytes, myelocytes, and metamyelocytes, is administered to the patient. Thereafter, the neutrophil precursors differentiate rapidly in vivo to replenish the supply of mature neutrophils for fighting infection. The **method** is used to reduce the neutropenic window between the time of myeloablative therapy and the time required for infused **stem** **cells** to proliferate and differentiate into mature neutrophils.

US PAT NO: 5,814,307 [IMAGE AVAILABLE] L4: 4 of 16
TITLE: **Method** for regulating **cell** growth, leukocyte differentiation and tumor **cell** growth using Oncostatin M to stimulate synthesis of IL-6

ABSTRACT:
The present invention relates to **methods** of using oncostatin M (OM). In particular, it relates to the use of OM to stimulate **interleukin** **6** (IL-6) synthesis in target **cells**, especially human endothelial **cells**. The resultant IL-6, in turn, may perform a variety of functions such as **cell** growth regulation, leukocyte differentiation, and tumor inhibition. Furthermore, the present invention also relates to the use of OM to treat cytopenias, including anemia and thrombocytopoiesis, and to increase tolerance to irradiation and cytotoxic drugs. Therefore, the **methods** of the invention may have a wide range of applications, including, but not limited to, the inhibition of tumor growth, the treatment of cytopenias, and to increase the tolerance to radio- and chemotherapy. OM may be used in combination with various cytokines, including erythropoietin, colony-stimulating factors, **interleukin**-**3** or **thrombopoietin**.

US PAT NO: 5,786,323 [IMAGE AVAILABLE] L4: 5 of 16
TITLE: Use of **stem** **cell** factor and soluble **interleukin**-**6** receptor to induce the development of **hematopoietic** **stem** **cells**

ABSTRACT:
Stem **cell** factor in combination with gp130 signaling supports proliferation, differentiation and terminal maturation of erythroid **cells** from normal human **hematopoietic** **stem** **cells**.

US PAT NO: 5,750,397 [IMAGE AVAILABLE] L4: 6 of 16
TITLE: Human **hematopoietic** **stem** **cell**

ABSTRACT:
Human **hematopoietic** **stem** **cells** are provided by separation of the **stem** **cells** from dedicated **cells**. The **stem** **cells** may than be maintained by regeneration in an appropriate growth medium. Means are provided for assaying for the **stem** **cells** as to their capability for producing members of each of the **hematopoietic** lineages.

US PAT NO: 5,744,361 [IMAGE AVAILABLE] L4: 7 of 16
TITLE: Expansion of human **hematopoietic** progenitor **cells** in a liquid medium

ABSTRACT:
The use of individual or combinations of cytokines, particularly IL-3, GM-CSF, and **c**-**kit** ligand are employed for long-term hematopoiesis in serum free **culture** in the absence of stromal **cells**. The **cultures** can be used for evaluating compounds and their effect on hematopoiesis, particularly as to lifetime and nature of differentiation. In addition, the expanded **cells** may be used for engraftment in a mammalian host or enhancement of particular **cell** lineages in a mammalian host. The subject systems may be used with any mammalian hemopoietic **cells**, but finds particular application with primates, more particularly humans.

US PAT NO: 5,728,581 [IMAGE AVAILABLE] L4: 8 of 16
TITLE: **Method** of expanding **hematopoietic** **stem** **cells**, reagents and bioreactors for use therein

ABSTRACT:
The present invention provides **methods** and bioreactors for expanding **stem** **cells** in a population of **cells** substantially enriched in **hematopoietic** **stem** **cells** and substantially free of stromal **cells**. The **method** comprising the steps of inoculating the population of **cells** in an expansion container in a volume of suitable medium such that the **cell** density is at least about 5,000 **cells**/1 mL and at an initial oxygen concentration of less than 8%; adding an effective amount of at least one cytokine to cause **stem** **cell** expansion; culturing the **cells** under suitable conditions such that the **cells** condition the medium; increasing the oxygen concentration to about 20%; exchanging the medium at a rate which allows expansion of the **stem** **cells**; and culturing the **cells** under conditions such that the **stem** **cells** are expanded. The present invention also provides a bioreactor constructed to accomodate the operational requirements for stroma-free **stem** **cell** expansion.

US PAT NO: 5,700,691 [IMAGE AVAILABLE] L4: 9 of 16
TITLE: **Method** for the preparation of in vitro-derived human neutrophil precursor **cells**

ABSTRACT:
A composition of human neutrophil precursor **cells** is disclosed wherein at least 16% of the **cells** are human myeloblasts and promyelocytes. The myeloblasts and promyelocytes are derived from human neutrophil progenitor **cells** that were obtained from peripheral blood, bone marrow or cord blood. The neutrophil precursor **cells** contain less than 5% colony forming units. Also disclosed are human neutrophil precursor **cells** made up of about 16% CD15+CD11b- **cells** and less than 5% colony forming units and **methods** of preparing these compositions.

US PAT NO: 5,643,761 [IMAGE AVAILABLE] L4: 10 of 16
TITLE: **Method** for generating a subtracted cDNA library and uses of the generated library

ABSTRACT:
This invention provides a **method** of generating a subtracted cDNA library of a **cell** comprising: a) generating a cDNA library of the **cell**; b) isolating double-stranded DNAs from the cDNA library; c) releasing the double-stranded cDNA inserts from the double-stranded DNAs; d) denaturing the isolated double-stranded cDNA inserts; e) hybridizing the denatured double-stranded cDNA inserts with a labelled

single-stranded nucleic acid molecules which are to be subtracted from the cDNA library; and f) separating the hybridized labeled single-stranded nucleic acid molecule from the double-stranded cDNA inserts, thereby generating a subtracted cDNA library of a **cell**.

US PAT NO: 5,635,388 [IMAGE AVAILABLE] L4: 11 of 16
TITLE: Agonist antibodies against the flk2/**flt3** receptor and uses thereof

ABSTRACT:
Agonist antibodies are disclosed which bind to the extracellular domain of the flk2/**flt3** receptor and thereby activate the intracellular kinase domain thereof. The labeled antibodies are useful as diagnostics for detecting the presence of the flk2/**flt3** receptor in primitive **hematopoietic** **cells** for example. The antibodies are able to cause primitive **hematopoietic** **cells** to proliferate and/or differentiate and thereby enhance repopulation of mature blood **cell** lineages in a mammal which has undergone chemo- or radiation therapy or bone marrow transplantation. The antibodies are further useful for treating mammals which have suffered a decrease in blood **cells** as a consequence of disease or a hemorrhage, for example.

US PAT NO: 5,635,387 [IMAGE AVAILABLE] L4: 12 of 16
TITLE: **Methods** and device for culturing human **hematopoietic** **cells** and their precursors

ABSTRACT:
Methods for increasing the number of human **hematopoietic** precursor **cells** in vitro are provided. The **methods** generally comprise (a) separating human **hematopoietic** precursor **cells** from mature **hematopoietic** **cells** present in a blood product; (b) inoculating the separated precursor **cells** into a **culture** vessel containing a **culture** medium comprising a nutritive medium and a source of growth factors at a density of between 1.times.10.sup.3 **cells**/ml and 4.times.10.sup.6 **cells**/ml; and (c) culturing the **cells** under conditions and for a time sufficient to increase the number of precursor **cells** relative to the number of such **cells** present in the blood product. The **culture** medium may also include a suitable amount of microcarrier beads. Suitable blood products include bone marrow, umbilical cord blood, and peripheral blood. A device for carrying out such **methods** is also provided.

US PAT NO: 5,610,056 [IMAGE AVAILABLE] L4: 13 of 16
TITLE: Use of **stem** **cell** factor **interleukin**-**6** and soluble **interleukin**-**6** receptor to induce the development of **hematopoietic** **stem** **cells**

ABSTRACT:
Stem **cell** factor in combination with **interleukin**-**6** and soluble **interleukin**-**6** receptor supports proliferation, differentiation and terminal maturation of erythroid **cells** from normal human **hematopoietic** **stem** **cells**.

US PAT NO: 5,599,703 [IMAGE AVAILABLE] L4: 14 of 16
TITLE: In vitro amplification/expansion of CD34.sup.+ **stem** and progenitor **cells**

ABSTRACT:
The present invention relates to a **method** of amplifying in vitro stemcells. In this **method** **hematopoietic** CD34.sup.+ **stem** and

progenitor **cells** are isolated from human bone marrow and contacted with endothelial **cells**. The contacted **stem** **cells** and endothelial **cells** are cultured in the presence of at least one cytokine in an amount sufficient to support amplification/expansion of the **hematopoietic** CD34.sup.+ **stem** and progenitor **cells**. This **method** produces increased yields of **hematopoietic** CD34.sup.+ **stem** and progenitor **cells** which can be used in human therapeutics.

US PAT NO: 5,409,825 [IMAGE AVAILABLE] L4: 15 of 16
TITLE: Expansion of human **hematopoietic** progenitor **cells** in a liquid medium

ABSTRACT:

A process for supporting **hematopoietic** progenitor **cells** in a **culture** medium which contains at least one cytokine effective for supporting the **cells**, and preferably, is essentially free of stromal **cells**.

US PAT NO: 5,332,672 [IMAGE AVAILABLE] L4: 16 of 16
TITLE: Prevention of ES **cell** differentiation by ciliary neurotrophic factor

ABSTRACT:
The present invention provides for a stable, biologically active CNTF/receptor complex, and hybrids or routants thereof. The invention is also based in part on the discovery that the CNTF/receptor complex promotes differentiation through a signal transduction pathway on target **cells** that do not express the CNTF receptor. The invention further provides for a specific CNTFR mutant that promotes signal transduction without binding CNTF. The invention also provides for a CNTF/receptor blocking mutant, a mutant possessing a high binding affinity to CNTF, but possessing no signal transducing function. The present invention also identifies receptor components shared by the IL-6, CNTF, **LIF** and OSM signal transduction pathways, and the initiation of signal transduction based upon the presence of such components. The present invention additionally provides for therapeutic and diagnostic applications dependant on the ability of the CNTF/receptor complex, hybrid or mutant to elicit a physiological response on the appropriate target **cell**.

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U.S. Patent & Trademark Office LOGOFF AT 15:05:35 ON 18 MAR 1999

L4 16 L3 AND ((INTERLEUKIN 3 OR IL3) OR (LEUKEMIA INHIBITORY FACT OR LIF) OR C-KIT)

=> d l4 ti,ab 1-16

US PAT NO: 5,861,315 [IMAGE AVAILABLE] L4: 1 of 16
TITLE: Use of **stem** **cell** factor and soluble **interleukin**-**6** receptor for the ex vivo expansion of **hematopoietic** multipotential **cells**

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US PAT NO: 5,610,056 [IMAGE AVAILABLE] L4: 13 of 16
TITLE: Use of **stem** **cell** factor **interleukin**-**6** and

s[redacted]ble **interleukin**-**6** receptor to induce the development of **hematopoietic** [redacted]em** **cells**

ABSTRACT:
Stem **cell** factor in combination with **interleukin**-**6** and soluble **interleukin**-**6** receptor supports proliferation, differentiation and terminal maturation of erythroid **cells** from normal human **hematopoietic** **stem** **cells**.

US PAT NO: 5,599,703 [IMAGE AVAILABLE] L4: 14 of 16
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US PAT NO: 5,409,825 [IMAGE AVAILABLE] L4: 15 of 16
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ABSTRACT:

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US PAT NO: 5,332,672 [IMAGE AVAILABLE] L4: 16 of 16
TITLE: Prevention of ES **cell** differentiation by ciliary neurotrophic factor

ABSTRACT:
The present invention provides for a stable, biologically active CNTF/receptor complex, and hybrids or routants thereof. The invention is also based in part on the discovery that the CNTF/receptor complex promotes differentiation through a signal transduction pathway on target **cells** that do not express the CNTF receptor. The invention further provides for a specific CNTFR mutant that promotes signal transduction without binding CNTF. The invention also provides for a CNTF/receptor blocking mutant, a mutant possessing a high binding affinity to CNTF, but possessing no signal transducing function. The present invention also identifies receptor components shared by the IL-6, CNTF, **LIF** and OSM signal transduction pathways, and the initiation of signal transduction based upon the presence of such components. The present invention additionally provides for therapeutic and diagnostic applications dependant on the ability of the CNTF/receptor complex, hybrid or mutant to elicit a physiological response on the appropriate target **cell**.

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? s hematopoeitic and stem and cell and (polynucleotide or DNA or transform
or ribozyme or antisense)

             67  HEMATOPOEITIC
         169548  STEM
        3025451  CELL
           6376  POLYNUCLEOTIDE
        1018521  DNA
          24591  TRANSFORM
           3087  RIBOZYME
          20940  ANTISENSE
      S1      2  HEMATOPOEITIC AND STEM AND CELL AND (POLYNUCLEOTIDE OR
                 DNA OR TRANSFORM OR RIBOZYME OR ANTISENSE)
? s hematopoietic and stem and cell and (polynucleotide or DNA or transform
or ribozyme or antisense)

          58095  HEMATOPOIETIC
         169548  STEM
        3025451  CELL
           6376  POLYNUCLEOTIDE
        1018521  DNA
          24591  TRANSFORM
           3087  RIBOZYME
          20940  ANTISENSE
      S2   3080  HEMATOPOIETIC AND STEM AND CELL AND (POLYNUCLEOTIDE OR
                 DNA OR TRANSFORM OR RIBOZYME OR ANTISENSE)
? s s1 and s2 and (mpl or flt3)

             2  S1
          3080  S2
          1500  MPL
           690  FLT3
      S3     1  S1 AND S2 AND (MPL OR FLT3)
? t s3/3,ab/1

>>>No matching display code(s) found in file(s): 342

 3/3,AB/1     (Item 1 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
(c) 1999 BIOSIS. All rts. reserv.

11845084   BIOSIS NO.: 199900091193
cDNA cloning of FRIL, a lectin from Dolichos lablab, that preserves
  hematopoeitic progenitors in suspension culture.

AUTHOR: Colucci Gabriella; Moore Jeffrey G; Feldman Michael; Chrispeels
  Maarten J(a)
AUTHOR ADDRESS: (a)Dep. Biol., Univ. California San Diego, La Jolla, CA
  92093-0116, USA

JOURNAL: Proceedings of the National Academy of Sciences of the United
States of America  96 (2):p646-650 Jan. 19, 1999
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Ex vivo culture of hematopoietic stem cells is
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limited by the inability of cytokines to maintain primitive cells without inducing proliferation, differentiation, and subsequent loss of repopulating capacity. We identified recently in extracts of kidney bean and hyacinth bean a mannose-binding lectin, called FRIL, and provide here evidence that this protein appears to satisfy properties of a **stem cell** preservation factor. FRIL was first identified based on its ability to stimulate NIH 3T3 cells transfected with **Flt3**, a tyrosine kinase receptor central to regulation of **stem** cells. Molecular characterization from polypeptide sequencing and identification of the cDNA of hyacinth bean FRIL shows 78% amino acid identity with a mannose-binding lectin of hyacinth beans. Treatment of primitive **hematopoietic** progenitors in suspension culture with purified hyacinth FRIL alone is able to preserve cells for 1 month without medium changes. In vitro progenitor assays for human **hematopoietic** cells cultured 3 weeks in FRIL displayed small blast-like colonies that were capable of serial replating and persisted even in the presence of cytokines known to induce differentiation. These results suggest that FRIL is capable of preserving primitive progenitors in suspension culture for prolonged periods. FRIL's clinical utility involving procedures for **stem cell** transplantation, tumor **cell** purging before autologous transplantation, and ex vivo cultures used for expansion and **stem cell** gene therapy currently are being explored.

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? ds

Set     Items   Description
S1          2   HEMATOPOEITIC AND STEM AND CELL AND (POLYNUCLEOTIDE OR DNA
             OR TRANSFORM OR RIBOZYME OR ANTISENSE)
S2       3080   HEMATOPOIETIC AND STEM AND CELL AND (POLYNUCLEOTIDE OR DNA
             OR TRANSFORM OR RIBOZYME OR ANTISENSE)
S3          1   S1 AND S2 AND (MPL OR FLT3)
? s mpl and ligand

           1500  MPL
         108469  LIGAND
      S4    444  MPL AND LIGAND
? s s4 and flt3

            444  S4
            690  FLT3
      S5     21  S4 AND FLT3
? s s5 and hematopoietic

             21  S5
          58095  HEMATOPOIETIC
      S6     12  S5 AND HEMATOPOIETIC
? t s6/3,ab/all

>>>No matching display code(s) found in file(s): 342

 6/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.

09735865   98370104
  Ex vivo expansion of cord blood progenitors.
  Piacibello W; Sanavio F; Severino A; Garetto L; Dane A; Gammaitoni L;
Aglietta M
  Department of Biomedical Sciences and Human Oncology, University of
Torino Medical School, Mauriziano Hospital, Candiolo, Italy.
ONCOEMAT@tin.it
  Vox Sang (SWITZERLAND) 1998, 74 Suppl 2 p457-62, ISSN 0042-9007
Journal Code: XLI
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
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Human umbilical cord blood contains abundant primitive and committed **hematopoietic** progenitors; in addition, the general availability and the ease of procurement make cord blood a very attractive alternative source of transplantable **hematopoietic** tissue. However, the major limitation to a widespread use of cord blood for transplantation lays in its limited volume. For such a reason, until now, cord blood transplant has been mainly restricted to children and small size adults. Ex vivo expansion of cord blood stem cells could make the use of cord blood transplant feasible also for adult patients. Recently we developed a stroma-free culture system in which a progressive, increasingly greater production of hemopoietic progenitors belonging to all the **hematopoietic** lineages was sustained for over six months. A similar sustained and prolonged expansion of the most primitive stem cells that can be detected in vitro (LTC-IC), was also documented. The extremely prolonged maintenance and the massive expansions suggest that extensive self-renewal and little differentiation can be triggered in vitro by **FLT3**/FLK2 **ligand** (FL) plus c-**mpl ligand** (Thrombopoietin) and this could represent a first step towards the implementation of clinical expansion-transplantation strategies.

6/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09579602 98322150

Thrombopoietin promotes the survival of murine **hematopoietic** long-term reconstituting cells: comparison with the effects of **FLT3**/FLK-2 **ligand** and interleukin-6.

Matsunaga T; Kato T; Miyazaki H; Ogawa M
Department of Veterans Affairs Medical Center, Charleston, SC 29401-5799, USA.

Blood (UNITED STATES) Jul 15 1998, 92 (2) p452-61, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: RO1 DK32294, DK, NIDDK; RO1 DK48714, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The effects of thrombopoietin (TPO; c-**mpl ligand**), **FLT3**/FLK-2 **ligand** (FL), and interleukin-6 (IL-6) on the survival of murine **hematopoietic** long-term reconstituting cells (LTRC) were studied by using lineage-negative, Sca-1-positive, c-kit-positive (Lin-Sca-1(+)c-kit+) marrow cells from 5-fluorouracil-treated mice. We tested the ability of these cytokines to maintain the viability of LTRC by transplanting the cultured cells to lethally irradiated Ly-5 congenic mice together with compromised marrow cells. As a single agent, only TPO could maintain the LTRC. Neither IL-6 nor FL was effective by itself, but they acted synergistically to maintain the LTRC. We examined whether the maintenance of LTRC by these cytokines was due to the survival of stem cells or was the result of active cell divisions and self-renewal. To monitor cell division, we used membrane dye PKH26. Enriched cells were stained with PKH26 on day 0 and incubated in suspension culture with TPO or with IL-6 and FL for 7 days. On day 7, PKH26(low) and PKH26(high) cells were prepared by sorting and their in vivo reconstituting abilities were tested by transplantation into lethally irradiated Ly-5 congenic mice together with compromised marrow cells. PKH26(high) populations cultured with both TPO alone and the combination of IL-6 and FL showed greater reconstitution activity than that of PKH26(low) populations. These data indicate that TPO alone and the combination of IL-6 and FL can support the survival of stem cells without stimulating their active cell proliferation.

6/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09424693 98140498

Thrombopoietin, steel factor and the **ligand** for **flt3**/flk2 interact to stimulate the proliferation of human **hematopoietic** progenitors in culture.

Kobayashi M; Laver JH; Lyman SD; Kato T; Miyazaki H; Ogawa M
Department of Veterans Affairs Medical Center, Charleston, SC 29401-5799, USA.

Int J Hematol (IRELAND) Dec 1997, 66 (4) p423-34, ISSN 0925-5710 Journal Code: A7F
Contract/Grant No.: DK32294, DK, NIDDK; DK/HL48714, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We have tested the effects of steel factor (SF) the **ligand** for **flt3**/flk2 (FL) and thrombopoietin (TPO, **Mpl ligand**), on the proliferation of primitive human bone marrow progenitors in serum-deprived culture. Varying combinations of SF, FL and TPO supported formation of only few colonies from CD34+/c-Kit(low)/CD38neg/low cells. However, the addition of interleukin 3 (IL-3) to the three cytokines significantly increased the number of colonies. When this population of cells was tested in suspension culture for one week for production of colony-forming cells there was synergism among SF, FL and TPO. Addition of IL-3 to the three cytokines further increased the number of erythroid colony-forming cells. The effects of these four factors on CD34+/c-Kit(low)/CD38high cells were merely additive. Studies of individual CD34+/c-Kit(low)/CD38neg/low cells demonstrated the direct effects of SF, FL and TPO. In the presence of SF, FL and TPO, approximately half of the individual CD34+/c-Kit(low)/CD38neg/low cells proliferated in seven day suspension culture. Addition of IL-3 to the combination of SF, FL and TPO did not increase the frequencies of proliferating clones, but increased the size of individual clones. These observations suggest that SF, FL and TPO play important roles in survival and proliferation of primitive human **hematopoietic** progenitors.

6/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09081903 97307591

Thrombopoietin directly and potently stimulates multilineage growth and progenitor cell expansion from primitive (CD34+ CD38-) human bone marrow progenitor cells: distinct and key interactions with the ligands for c-kit and **flt3**, and inhibitory effects of TGF-beta and TNF-alpha.

Ramsfjell V; Borge OJ; Cui L; Jacobsen SE
Hipple Cancer Research Center, Dayton, OH 45439, USA. Veslemoy.Ramsfjell@med.lu.se

J Immunol (UNITED STATES) Jun 1 1997, 158 (11) p5169-77, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Thrombopoietin (Tpo) is a primary regulator of megakaryocyte and platelet production. However, studies in c-**mpl**-deficient mice suggest that Tpo might also play an important role in early hemopoiesis. Here, the direct ability of Tpo to stimulate stroma-independent growth, multilineage differentiation, and progenitor cell expansion from single primitive CD34+ CD38- human bone marrow cells was investigated. Tpo alone stimulated limited clonal growth, but synergized with c-kit **ligand** (KL), **flt3 ligand** (FL), or IL-3 to potently enhance clonogenic growth. Whereas KL and FL in combination stimulated the clonal growth of only 3% of CD34+ CD38- cells, 40% of CD34+ CD38- cells were recruited by KL+FL+Tpo, demonstrating that Tpo promotes the growth of a high fraction of CD34+ CD38- progenitor cells. Additional cytokines (IL-3, IL-6, and erythropoietin (Epo)) did not significantly enhance clonal growth above that observed in response to KL+FL+Tpo. In contrast, Tpo enhanced clonogenic growth in response to KL+FL+IL-3+IL-6+Epo by as much as 80%,

implicating a key role for this cytokine in early hematopoiesis. Importantly, we also demonstrate that the majority of Tpo-recruited CD34+ CD38- progenitor cells have a multilineage differentiation potential, and that Tpo promotes prolonged expansion of multipotent progenitors. Specifically, whereas progenitor cells were reduced in cultures containing only KL+FL, addition of Tpo resulted in 40-fold expansion of multipotent progenitors following a 14-day incubation. Finally, we identified inhibitors of Tpo-induced progenitor cell growth, in that TGF-beta as well as TNF-alpha almost completely abrogated the growth of CD34+ CD38- progenitor cells in response to Tpo alone as well as KL+FL+Tpo.

6/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09029872 97251010
Thrombopoietin augments ex vivo expansion of human cord blood-derived **hematopoietic** progenitors in combination with stem cell factor and **flt3 ligand**.
Ohmizono Y; Sakabe H; Kimura T; Tanimukai S; Matsumura T; Miyazaki H; Lyman SD; Sonoda Y
Department of Pediatrics, Kyoto Prefectural University of Medicine, Japan.
Leukemia (ENGLAND) Apr 1997, 11 (4) p524-30, ISSN 0887-6924
Journal Code: LEU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We studied the effects of stem cell factor (SCF) and **flt3 ligand** (FL) on the ex vivo expansion of human umbilical cord blood (CB)-derived CD34+ cells in combination with various cytokines, including interleukin (IL)-3, IL-6, IL-11, and c-**Mpl ligand** (thrombopoietin, TPO), in a short-term serum-free liquid suspension culture system. Among the two-factor combinations tested, SCF plus IL-3 most effectively expanded committed progenitor cells, including mixed colony-forming units (CFU-Mix). The expansion efficiency (EE) of FL for each progenitor was inferior to that of SCF in the presence of various cytokines, except TPO. IL-6 significantly increased the EE for granulocyte/macrophage colony-forming units (CFU-GM) obtained with SCF + IL-3 or FL + IL-3. Interestingly, TPO markedly augmented the EE for committed progenitors, including CFU-GM, erythroid burst-forming units (BFU-E), and CFU-Mix, in the presence of SCF + IL-3 or FL + IL-3. The combinations of SCF + IL-3 + TPO + IL-6 or IL-11 maximally stimulated the expansion of committed progenitors. The maximum EE for CFU-GM, BFU-E, and CFU-Mix was respectively 197-fold (day 14), 60-fold (day 7) and 51-fold (day 14). Other combinations of cytokines without IL-3 failed to expand effectively these committed progenitors. Our data demonstrate that it is possible to expand human CB-derived committed progenitors in vitro using SCF or FL with several other cytokines including TPO, and that IL-3 is the key cytokine promoting the expansion of human **hematopoietic** progenitors in the presence of SCF or FL.

6/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08867293 97099269
Soluble thrombopoietin receptor (**Mpl**) and granulocyte colony-stimulating factor receptor directly stimulate proliferation of primitive **hematopoietic** progenitors of mice in synergy with steel factor or the **ligand** for **Flt3**/Flk2.
Ku H; Hirayama F; Kato T; Miyazaki H; Aritomi M; Ota Y; D'Andrea AD; Lyman SD; Ogawa M
Department of Medicine, Medical University of South Carolina, Charleston,

USA.
Blood (UNITED STATES) Dec 1 1996, 88 (11) p4124-31, ISSN 0006-4971
Journal Code: A8G
Contract/Grant No.: DK32294, DK, NIDDK; DK/HL48714, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

In an effort to establish the specificity of the thrombopoietin (TPO) effects on murine multipotential progenitors, we tested the effects of soluble TPO receptor (sTPOR; sMpl) on multilineage colony formation that was supported by a combination of TPO and steel factor (SF). Surprisingly, sTPOR did not suppress colony formation from primitive progenitors. This led to the discovery that sTPOR synergizes with SF or **Flt3**/Flk2 **ligand** (FL) to support the formation of various types of **hematopoietic** colonies including multilineage colonies. The colonies supported by the combination of sTPOR and SF were capable of expressing both myeloid and B-lymphoid potentials. Studies using micromanipulation and serum-free culture showed that the effects of sTPOR and SF on the primitive progenitors are direct, not mediated by contaminating stromal cells, and not dependent on factors present in the serum. TPOR belongs to the cytokine receptor group that includes granulocyte colony-stimulating factor receptor (G-CSFR) and erythropoietin receptor (EPOR). Therefore, we tested the effects of sG-CSFR and sEPOR on primitive progenitors. sG-CSFR, but not sEPOR, was able to synergize with SF or FL in supporting the proliferation of primitive progenitors. The direct effects of the soluble receptors appear to be mediated through interactions with their respective membrane-bound receptors expressed on the primitive **hematopoietic** progenitors.

6/3,AB/7 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11619128 BIOSIS NO.: 199800401036
Ex vivo expansion of cord blood progenitors.

AUTHOR: Piacibello W(a); Sanavio F; Severino A; Garetto L; Dane A; Gammaitoni L; Aglietta M
AUTHOR ADDRESS: (a)Dep. Biomed. Sci. Hum. Oncol., Clin. Med. I, Via Genova 3, 10126 Torino, Italy

JOURNAL: Vox Sanguinis 74 (SUPPL. 2):p457-462 June, 1998
ISSN: 0042-9007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Human umbilical cord blood contains abundant primitive and committed **hematopoietic** progenitors; in addition, the general availability and the ease of procurement make cord blood a very attractive alternative source of transplantable **hematopoietic** tissue. However, the major limitation to a widespread use of cord blood for transplantation lays in its limited volume. For such a reason, until now, cord blood transplant has been mainly restricted to children and small size adults. Ex vivo expansion of cord blood stem cells could make the use of cord blood transplant feasible also for adult patients. Recently we developed a stroma-free culture system in which a progressive, increasingly greater production of hemopoietic progenitors belonging to all the **hematopoietic** lineages was sustained for over six months. A similar sustained and prolonged expansion of the most primitive stem cells that can be detected in vitro (LTC-IC), was also documented. The extremely prolonged maintenance and the massive expansions suggest that extensive self-renewal and little differentiation can be triggered in vitro by **FLT3**/FLK2 **ligand** (FL) plus c-**mpl ligand** (Thrombopoietin) and this could represent a first

step towards the implementation of clinical expansion-transplantation strategies.

6/3,AB/8 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11576593 BIOSIS NO.: 199800357289
Thrombopoietin promotes the survival of murine **hematopoietic** long-term reconstituting cells: Comparison with the effects of **FLT3** /FLK-2 **ligand** and interleukin-6.

AUTHOR: Matsunaga Takuya; Kato Takashi; Miyazaki Hiroshi; Ogawa Makio(a)
AUTHOR ADDRESS: (a)Ralph H. Johnson Med. Center, 109 Bee St., Charleston, SC 29401-5799, USA

JOURNAL: Blood 92 (2):p452-461 July 15, 1998
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effects of thrombopoietin (TPO; c-**mpl ligand**), **FLT3**/FLK-2 **ligand** (FL), and interleukin-6 (IL-6) on the survival of murine **hematopoietic** long-term reconstituting cells (LTRC) were studied by using lineage-negative, Sca-1-positive, c-kit-positive (Lin-Sca-1+c-kit+) marrow cells from 5-fluorouracil-treated mice. We tested the ability of these cytokines to maintain the viability of LTRC by transplanting the cultured cells to lethally irradiated Ly-5 congenic mice together with compromised marrow cells. As a single agent, only TPO could maintain the LTRC. Neither IL-6 nor FL was effective by itself, but they acted synergistically to maintain the LTRC. We examined whether the maintenance of LTRC by these cytokines was due to the survival of stem cells or was the result of active cell divisions and self-renewal. To monitor cell division, we used membrane dye PKH26. Enriched cells were stained with PKH26 on day 0 and incubated in suspension culture with TPO or with IL-6 and FL for 7 days. On day 7, PKH26low and PKH26high cells were prepared by sorting and their in vivo reconstituting abilities were tested by transplantation into lethally irradiated Ly-5 congenic mice together with compromised marrow cells. PKH26high populations cultured with both TPO alone and the combination of IL-6 and FL showed greater reconstitution activity than that of PKH26low- populations. These data indicate that TPO alone and the combination of IL-6 and FL can support the survival of stem cells without stimulating their active cell proliferation.

6/3,AB/9 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10733444 BIOSIS NO.: 199799354589
Thrombopoietin augments ex vivo expansion of human cord blood derived **hematopoietic** progenitors in combination with stem cell factor and **FLT3 ligand**.

AUTHOR: Sonoda Y(a); Ohmizono Y; Kimura T; Sakabe H; Tanimukai S; Lyman S D ; Abe T
AUTHOR ADDRESS: (a)Dep. Hygiene, Kyoto Prefectural Univ. Med., Kyoto, Japan

JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p602A 1996

CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996

ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

6/3,AB/10 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10732817 BIOSIS NO.: 199799353962
Soluble thrombopoietin receptor (**MPL**) and G-CSF receptor directly stimulate proliferation of primitive **hematopoietic** progenitors of mice in synergy with steel factor or the **ligand** for **FLT3** /FLK2.

AUTHOR: Ku H(a); Hirayama F; Kato T; Miyazaki H; Aritomi M; Ota Y; D'Andrea A D; Lyman S D; Ogawa M
AUTHOR ADDRESS: (a)Dep. Med., Med. Univ. S.C., Charleston, SC, USA

JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2):p445A 1996

CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English

6/3,AB/11 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10692228 BIOSIS NO.: 199799313373
Soluble thrombopoietin receptor (**Mpl**) and granulocyte colony-stimulating factor receptor directly stimulate proliferation of primitive **hematopoietic** progenitors of mice in synergy with steel factor or the **ligand** for **Flt3**/Flk2.

AUTHOR: Ku Hsun; Hirayama Fumiya; Kato Takashi; Miyazaki Hiroshi; Aritomi Masaharu; Ota Yoshimi; D'Andrea Alan D; Lyman Stewart D; Ogawa Makio
AUTHOR ADDRESS: VA Med. Center, 109 Bee St., Charleston, SC 29401-5799, USA

JOURNAL: Blood 88 (11):p4124-4131 1996
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In an effort to establish the specificity of the thrombopoietin (TPO) effects on murine multipotential progenitors, we tested the effects of soluble TPO receptor (sTPOR; sMpl) on multilineage colony formation that was supported by a combination of TPO and steel factor (SF). Surprisingly, sTPOR did not suppress colony formation from primitive progenitors. This led to the discovery that sTPOR synergizes with SF or **Flt3**/Flk2 **ligand** (FL) to support the formation of various types of **hematopoietic** colonies including multilineage colonies. The colonies supported by the combination of sTPOR and SF were capable of expressing both myeloid and B-lymphoid potentials. Studies using micromanipulation and serum-free culture showed that the effects of sTPOR and SF on the primitive progenitors are direct, not mediated by contaminating stromal cells, and not dependent on factors present in the serum. TPOR belongs to the cytokine receptor group that includes granulocyte colony-stimulating factor receptor (G-CSFR) and erythropoietin receptor (EPOR). Therefore, we tested the effects of sG-CSFR and sEPOR on primitive progenitors. sG-CSFR, but not sEPOR, was

able to synergize with SF or FL in supporting the proliferation of primitive progenitors. The direct effects of the soluble receptors appear to be mediated through interactions with their respective membrane-bound receptors expressed on the primitive **hematopoietic** progenitors.

6/3,AB/12 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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10551973 BIOSIS NO.: 199699173118
Effect of C-**mpl ligand** and **Flt3-ligand** on the regulation of human **hematopoietic** bone marrow and cord blood CD34+ progenitor cells growth.

AUTHOR: Garetto L(a); Sanavio F; Severino A; Aglietta M; Piacibello W
AUTHOR ADDRESS: (a)Dep. Biomed. Sci. Human Oncol., Torino, Italy

JOURNAL: Experimental Hematology (Charlottesville) 24 (9):p1071 1996

CONFERENCE/MEETING: 25th Annual Meeting of the International Society for Experimental Hematology New York, New York, USA August 23-27, 1996
ISSN: 0301-472X
RECORD TYPE: Citation
LANGUAGE: English

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? s hematopoietic and transform? and (vector or ribozyme or antisense)

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         107989  VECTOR
           3087  RIBOZYME
          20940  ANTISENSE
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                 ANTISENSE)
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        3025451  CELL
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 14/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.

09282042   97462640
  Efficient retrovirus-mediated gene transfer of dendritic cells generated
from CD34+ cord blood cells under serum-free conditions.
  Bello-Fernandez C; Matyash M; Strobl H; Pickl WF; Majdic O; Lyman SD;
Knapp W
  Vienna International Research Cooperation Center at Novartis
Forschungsinstitut, University of Vienna, Austria.
  Hum Gene Ther (UNITED STATES) Sep 20 1997, 8 (14) p1651-8, ISSN
1043-0342 Journal Code: A12
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE
  A retroviral-vector encoding the low affinity nerve growth factor
receptor (LNGFR) was used to transduce dendritic cells (DCs) generated from
CD34+ cord blood (CB) progenitor cells under serum-free conditions.
Transduction efficiency was monitored by flow cytometry (FACS) using a
specific monoclonal antibody. Prior to retroviral infections, CD34+ CB
cells were stimulated for 60 h in a serum-free medium containing a DC
differentiation inducing cytokine cocktail: stem cell
factor (SCF), granulocyte/macrophage-colony stimulating factor (GM-CSF),
tumor necrosis factor alpha (TNFalpha), and transforming growth
factor beta 1 (TGF-beta1). Addition of flt3-ligand (FL) to the
aforementioned growth factors significantly enhanced cell expansion
(41.7+/-11.5 fold vs. 22.5+/-4.7 fold without FL) and generation of CD1a+
DCs (mean 45.7+/-9.8% vs. 28+/-6.5% without FL, n = 4,p = 0.01).
Furthermore, FL significantly increased the proportion of CD1a+LNGFR+ cells
(mean 10%+/-4.4% vs. 6%+/-2.4 without FL n = 4, p = 0.03). When serum-free
viral supernatants were used to infect DCs progenitors under entirely
serum-free conditions and with the most potent cytokine combination,
approximately one-third of the CD1a+ DCs generated co-expressed the LNGFR
gene. Moreover, the transduced gene was also identified in more mature
CD1a+CD80+ and CD1a+CD86+ DCs after 12-14 days of culture. In addition,
transduced CD1a+ DCs maintained their functional properties, stimulating
allogeneic T cells with similar efficiency as nontransduced CD1a+ DCs.
Thus, the serum-free system described allows efficient generation and
transduction of CD1a+ DCs derived from CD34+ progenitor cells and may be
very useful for future therapeutic applications of DCs.


 14/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09198233 97419188
Altered proliferative response by T lymphocytes of Ly-6A (Sca-1) null mice.
Stanford WL; Haque S; Alexander R; Liu X; Latour AM; Snodgrass HR; Koller BH; Flood PM
Department of Medicine, University of North Carolina, Chapel Hill, North Carolina 27599-7455, USA.
J Exp Med (UNITED STATES) Aug 29 1997, 186 (5) p705-17, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: R01DK-4351701, DK, NIDDK; PO1DK-38103, DK, NIDDK; R01DE-09426, DE, NIDR; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Ly-6A is a murine antigen which is implicated in lymphocyte activation and may be involved in activation of **hematopoietic stem** cells. Antibody cross-linking studies and **antisense** experiments have suggested that Ly-6A is a lymphocyte coactivation molecule. To better understand the function of Ly-6A, we used gene targeting to produce Ly-6A null mice which are healthy and have normal numbers and percentages of **hematopoietic** lineages. However, T lymphocytes from Ly-6A-deficient animals proliferate at a significantly higher rate in response to antigens and mitogens than wild-type littermates. In addition, Ly-6A mutant splenocytes generate more cytotoxic T lymphocytes compared to wild-type splenocytes when cocultured with alloantigen. This enhanced proliferation is not due to alterations in kinetics of response, sensitivity to stimulant concentration, or **cytokine** production by the T **cell** population, and is manifest in both in vivo and in vitro T **cell** responses. Moreover, T cells from Ly-6A-deficient animals exhibit a prolonged proliferative response to antigen stimulation, thereby suggesting that Ly-6A acts to downmodulate lymphocyte responses.

14/3,AB/3 (Item 3 from file: 155)

08773625 96380158
Increased stable retroviral gene transfer in early **hematopoietic** progenitors released from quiescence.
Hatzfeld A; Batard P; Panterne B; Taieb F; Hatzfeld J
Centre National de Recherche Scientifique, Villejuif, France.
Hum Gene Ther (UNITED STATES) Jan 20 1996, 7 (2) p207-13, ISSN 1043-0342 Journal Code: A12
Languages: ENGLISH
Document type: JOURNAL ARTICLE
It has been previously demonstrated that prestimulation with cytokines could improve gene transfer in **hematopoietic** progenitors. However, we have shown that no combination of cytokines so far tested is able to release rapidly in vitro the **stem cell** compartment from quiescence unless an autocrine **transforming** growth factor-beta 1 (TGF-beta 1) is blocked by specific oligonucleotide **antisense** or antiserum (Hatzfeld et al., 1991, J. Exp. Med., 174, 925). We now report that a 10-hr **cytokine** prestimulation of SBA-CD34high human umbilical cord blood progenitors increases retrovirally mediated transfer of the nls-lacZ reporter gene from 1% to 23.8% and addition of anti-TGF-beta serum doubles this increase (47.3%). Interestingly, the effect of anti-TGF-beta preincubation on gene transfer is most effective on the most immature progenitors, which develop into high proliferative potential mixed colonies with 1-2 x 10(5) cells. Anti-TGF-beta serum pretreatment increases gene transfer in these early colony-forming units granulocyte-erythroid-megakaryocyte-macrophage (CFU-GEMM) from 54.1% to 93.3%. It augments significantly the stability of gene expression in all subpopulations of mixed colonies. Colonies obtained after pretreatment with anti-TGF-beta serum are larger and the expression of the stably integrated recombinant provirus does not

reduce their size. This prestimulation method provides a substantial improvement for gene transfer efficiency within the quiescent **stem cell** compartment that is responsible for long-term engraftment.

14/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08716236 96234659
Stem cell factor as a survival and growth factor in human normal and malignant hematopoiesis.
Hassan HT; Zander A
Department of Hematology and Oncology, Hamburg University Hospital Eppendorf, Germany.
Acta Haematol (SWITZERLAND) 1996, 95 (3-4) p257-62, ISSN 0001-5792 Journal Code: 0S8
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Stem cell factor (SCF) is an essential **hematopoietic cytokine** that interacts with other cytokines to preserve the viability of **hematopoietic stem** and progenitor cells, to influence their entry into the **cell** cycle and to facilitate their proliferation and differentiation. SCF on its own cannot drive noncycling **hematopoietic** progenitor cells into the **cell** cycle but does prevent their apoptotic death. SCF when combined with other cytokines increases the cloning efficacy of **hematopoietic** progenitor cells from all lineages. SCF also stimulates the growth of CD34+ leukemic progenitor cells from most patients with acute myeloid leukemia (AML). The mRNA expression of the SCF receptor c-kit has been shown to be significantly increased in all fresh AML blast cells compared with normal controls (healthy volunteers), in particular CD34+ cells. Two inhibitory cytokines, **transforming** growth factor-beta and interleukin-4, decreased c-kit expression, whereas tumor necrosis factor-alpha increased c-kit expression, but chemotherapeutic drugs showed no effect on c-kit expression, but chemotherapeutic drugs showed no effect on c-kit expression in AML cells. Apoptosis has been shown to be directly related to a high complete remission rate in AML patients following induction therapy. Since SCF has been shown to stimulate the proliferation of mainly CD34+ AML cells, we have investigated whether the poor response of patients with CD34+ myeloid leukemia cells to chemotherapy could be due to SCF-induced resistance to apoptosis. The effect of SCF on the apoptosis induced by chemotherapeutic drugs commonly used in the treatment of AML - cytarabine, daunorubicin and carboplatin - was examined in human CD34+ myeloid leukemia cells in serum-free cultures. SCF significantly reduced the induced apoptosis by more than 50% in all CD34+ human leukemia cells treated by any of the three chemotherapeutic drugs. Antibodies blocking c-kit reversed the significant inhibitory effect of SCF on chemotherapy-induced apoptosis, confirming the role of SCF in the resistance to chemotherapy-induced apoptosis in CD34+ human leukemia. These results suggest that the poor response of patients with CD34+ leukemia cells could be at least partially due to less chemotherapy-induced apoptosis resulting from protection by SCF as an adjuvant mechanism for drug resistance in myeloid leukemia. We conclude that an **antisense** strategy to block c-kit expression in AML blast cells may prove valuable for decreasing the chemoresistance of AML patients. The abrogation of leukemic resistance to apoptotic death through anti-SCF/c-pit expression combined with chemotherapy offers potential for designing novel therapeutic approaches for refractory AML patients.

14/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08693770 96219639

Leukemia inhibitory factor upregulates **cytokine** expression by a murine stromal **cell** line enabling the maintenance of highly enriched competitive repopulating **stem** cells.

Szilvassy SJ; Weller KP; Lin W; Sharma AK; Ho AS; Tsukamoto A; Hoffman R; Leiby KR; Gearing DP

Department of Cell Biology, SyStemix, Inc, Palo Alto, CA 94304, USA.

Blood (UNITED STATES) Jun 1 1996, 87 (11) p4618-28, ISSN 0006-4971 Journal Code: A8G

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Attempts to maintain or expand primitive **hematopoietic stem** cells in vitro without the concomitant loss of their differentiative and proliferative potential in vivo have largely been unsuccessful. To investigate this problem, we compared the ability of three cloned bone marrow (BM) stromal **cell** lines to support the growth of primitive Thy-1lo Sca-1+H-2Khi cells isolated by fluorescence-activated **cell** sorting from the BM of Ly-5.2 mice treated 1 day previously with 5-fluorouracil. Sorted cells were highly enriched in cobblestone area-forming cells (CAFC), but their frequency was dependent on the stromal **cell** lines used in this assay (1 per 45 cells on SyS-1; 1 per 97 cells on PA6). In the presence of recombinant leukemia inhibitory factor (LIF), CAFC cloning efficiency was increased to 1 per 8 cells on SyS-1 and 1 per 11 cells on PA6, thus showing the high clonogenicity of this primitive **stem cell** population. More primitive **stem** cells with competitive repopulating potential were measured by injecting the sorted cells into lethally irradiated Ly-5.1 mice together with 10(5) radioprotective Ly-5.1 BM cells whose long-term repopulating ability has been "compromised" by two previous cycles of marrow transplantation and regeneration. Donor-derived lymphocytes and granulocytes were detected in 66% of animals injected with 50 sorted cells. To quantitate the maintenance of competitive repopulating units (CRU) by stromal cells, sorted cells were transplanted at limiting dilution before and after being cultured for 2 weeks on adherent layers of SyS-1, PA6, or S17 cells. CRU represented 1 per 55 freshly sorted cells. CRU could be recovered from cocultures supported by all three stromal **cell** lines, but their numbers were approximately-sevenfold less than on day 0. In contrast, the addition of LIF to stromal cultures improved CRU survival by 2.5-fold on S17 and PA6 cells (approximately two-fold to threefold decline), and enabled their maintenance on SyS-1. LIF appeared to act indirectly, because alone it did not support the proliferation of Thy-1lo Sca-1+H-2Khi cells in stroma-free cultures. Polymerase chain reaction (RT-PCR) analysis revealed that Interleukin-1beta (IL-1 beta) IL-2, IL-6, granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor, **transforming** growth factors, LIF, and Steel Factor (SLF) mRNAs were upregulated in SyS-1 within 1 to 6 hours of LIF-stimulation. To determine if increased expression of SLF by LIF-stimulated SyS-1 cells could account for their capacity to support **stem** cells, sorted calls were cocultured on simian CV-E cells that were transfected with an expression **vector** encoding membrane-bound SLF, or supplemented with soluble SLF. In both cases, SLF synergized with IL-6 produced endogenously by CV-E cells enabling CAFC growth equivalent to that on LIF-stimulated SyS-1. CAFC development on LIF-stimulated SyS-1 could also be completely abrogated by an anti-SLF antibody. These data provide evidence for a role of LIF in the support of long-term repopulating **stem** cells by indirectly promoting **cytokine** expression by BM stroma. Furthermore, we have used quantitative assays to show a maintenance of CRU numbers, with retention of in vivo function following ex vivo culture.

14/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08648408 95383641

Early CD34high cells can be separated into KIThigh cells in which

transforming growth factor-beta (TGF-beta) downmodulates c-kit and KITlow cells in which anti-TGF-beta upmodulates c-kit.

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Blood (UNITED STATES) Sep 1 1995, 86 (5) p1729-35, ISSN 0006-4971 Journal Code: A8G

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We have previously shown that early human CD34high **hematopoietic** progenitors are maintained quiescent in part through autocrine **transforming** growth factor-beta 1 (TGF-beta 1). We also demonstrated that, in the presence of interleukin-3, interleukin-6, granulocyte colony-stimulating factor, and erythropoietin, TGF-beta 1 **antisense** oligonucleotides or anti-TGF-beta serum have an additive effect with KIT ligand (Steel factor [SF]), which suggests that they control different pathways of regulation in these conditions. This finding also suggests that autocrine TGF-beta 1 might suppress c-kit expression in primitive human **hematopoietic** progenitors. We have now distinguished two subpopulations of CD34high cells. One subpopulation expresses a c-kit mRNA that can be downmodulated by exogenous TGF-beta 1 within 6 hours. Another subpopulation of early CD34high cells expresses a low or undetectable level of c-kit mRNA, but its expression can be upmodulated within 6 hours by anti-TGF-beta. These effects disappear 48 hours after induction and cannot be maintained longer than 72 hours, even if TGF-beta 1 or anti-TGF-beta serum are added every day. Similar kinetics, although delayed, are observed with KIT protein expression. On the contrary, no specific effect of TGF-beta 1 was observed on c-fms, GAPDH, and transferrin receptor gene expression in these early progenitors. These results clarify the complex interaction between TGF-beta 1 and SF in normal early **hematopoietic** progenitors. SF does not switch off the TGF-beta 1 inhibitory pathway. Autocrine TGF-beta 1 appears to maintain these cells in a quiescent state, suppressing **cell** division by downmodulating the receptor of SF, a key **cytokine** costimulator of early progenitors.

14/3,AB/7 (Item 7 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08423785 95376803

IL-7 enhancement of antigen-driven activation/expansion of HIV-1-specific cytotoxic T lymphocyte precursors (CTLp).

Ferrari G; King K; Rathbun K; Place CA; Packard MV; Bartlett JA; Bolognesi DP; Weinhold KJ

Department of Surgery, Duke Centre for AIDS Research, Duke University Medical Centre, Durham, NC 27710-2996, USA.

Clin Exp Immunol (ENGLAND) Aug 1995, 101 (2) p239-48, ISSN 0009-9104 Journal Code: DD7

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Languages: ENGLISH

Document type: JOURNAL ARTICLE

CD8+ cytotoxic T lymphocytes are an important component in the immunologic control of human viral diseases. IL-7, a stromal **cell** -derived **cytokine**, has been demonstrated to enhance both anti-tumour and anti-viral CTL as well as lymphokine-activated killer (LAK) activity. We studied the ability of IL-7 to support the activation and the growth of in vitro antigen-specific CTL precursors (CTLp) present in peripheral blood mononuclear cells (PBMC) from HIV-infected patients. Results from these studies demonstrate that inclusion of IL-7 in a vaccinia/HIV-1 **vector** -based stimulation strategy greatly augmented overall CTL reactivities, whereas addition of IL-7 to unstimulated cultures failed to induce any significant anti-viral cytolytic activity. In four of six patients, HIV-specific lytic activities were significantly higher in cultures

stimulated with antigen plus IL-7 compared with in vitro stimulation (IVS) with antigen alone. Cytotoxic activity was principally mediated by CD8+ effector cells, and CD3+/CD8+ **cell** expansion was increased by 2.7-fold in the presence of IL-7. In PBMC from seronegative donors, IL-7 enhanced anti-vaccinia CTL activities with less effect on **cell** proliferation. Furthermore, anti-gag CTL frequencies determined by limiting dilution analysis were increased by 2- and 10-fold in two asymptomatic patients following IVS plus IL-7 compared with antigen stimulation alone. Cytofluorimetric analysis revealed that IL-7 preferentially expanded CD8 memory cells (CD45RO+) and CD8+ lymphocytes expressing activation molecules. IL-7 was also able to support the growth of CD4+ lymphocytes, while having no effect on natural killer (NK)/K lymphocytes. Taken together, these data suggest that IL-7 acts cooperatively with the antigen supporting in vitro maturation of CTLp into functional cytotoxic effectors. Thus IL-7 may be an important biologic entity to consider as part of future immune-based therapies in which ex vivo expansion of antigen-driven CTL is an important determinant.

14/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06950169 92013783

Leukemia inhibitory factor improves survival of retroviral **vector** -infected **hematopoietic stem** cells in vitro, allowing efficient long-term expression of **vector**-encoded human adenosine deaminase in vivo.

Fletcher FA; Moore KA; Ashkenazi M; De Vries P; Overbeek PA; Williams DE; Belmont JW

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J Exp Med (UNITED STATES) Oct 1 1991, 174 (4) p837-45, ISSN 0022-1007 Journal Code: I2V

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Document type: JOURNAL ARTICLE

Low recovery and poor retroviral **vector** infection efficiency of **hematopoietic stem** cells has hindered application of gene therapy for disease affecting blood-forming tissues. Developmental restriction (or death) of **stem** cells during ex vivo infection has contributed to these difficulties. In these studies we report that the **cytokine** leukemia inhibitory factor (LIF) directly or indirectly supported the survival of **hematopoietic stem** cells during culture of bone marrow with **vector**-producing fibroblasts, resulting in efficient recovery of **stem** cells able to compete for engraftment in irradiated recipient animals. The infection efficiency of **hematopoietic stem** cells recovered from these cultures was approximately 80%; and all recipients (20/20) of the LIF-treated marrow were stably engrafted with the progeny of provirus-bearing **stem** cells. Expression of **vector**-encoded human adenosine deaminase (hADA) was detected in all recipients at levels averaging 15-50% of endogenous murine ADA in all their hematolymphoid tissues. Survival of **stem** cells in untreated cultures was approximately 10% of that observed from LIF-treated cultures, resulting in poor engraftment of recipient animals with transplanted cells. The infection efficiency of the few **stem** cells recovered from untreated cultures, however, was high (approximately 80%), suggesting that LIF did not have an effect on infection efficiency per se, but acted at the level of **stem cell** survival. Consistent with the poor engraftment observed in the control animals, expression of **vector**-encoded ADA was only approximately 4-20% of the endogenous levels. These results support the postulated role of LIF as a regulator of hematopoiesis and suggest that **cytokine** stimulation can positively affect inefficient retroviral **vector** transduction in **hematopoietic stem** cells.

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>>>No matching display code(s) found in file(s): 342

 15/3,AB/1      (Item 1 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
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11867777   BIOSIS NO.: 199900113886
Transduction kinetics of non-human primate immuno-selected CD34+ cells
  using retroviral and lentiviral vectors that express the green
  fluorescent protein.

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JOURNAL: Blood  92 (10 SUPPL. 1 PART 1-2):p376B Nov. 15, 1998

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             0  RETRO(W)NECTIN
         58095  HEMATOPOIETIC
    S16      0  RETRO(W)NECTIN AND HEMATOPOIETIC
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